REMARKS

Claims 1-51 are pending. Claim 41 has previously been withdrawn from consideration and is canceled herein without prejudice or disclaimer. Claims 1 to 40, 42 to 47 and 49 stand variously rejected under 35 U.S.C. § 112, first paragraph, enablement.

Applicants acknowledge with appreciation that the rejections under 35 U.S.C. § 112, first paragraph, written description and 35 U.S.C. § 112, second paragraph have been withdrawn. Applicants also gratefully acknowledge that claims 48 and 50-51 are allowable.

Claims 1, 36 and 49 were previously amended to correct typographical errors and for clarity and claim 41 was previously canceled. By amendment herein, claim 1 now indicates that the expression cassette includes a sequence encoding an immunogenic HIV Pol polypeptide as described, for example, on page 14, line 19 to page 15, line 14; and in Section 2.4.1. The amendment is made to expedite prosecution and are not made for reasons related to patentability. No new matter has been added as a result of these amendments and entry thereof is respectfully requested.

In view of the following remarks and foregoing amendments, Applicants respectfully request reconsideration of the application.

Formal Drawings

Enclosed herewith for filing are 23 Sheets of formal drawings. These formal drawings include changes required by the Notice of Draftperson's Patent Drawing Review attached to Paper No. 9.

Claim Objections

Claims 1, 36 and 49 were objected to for having a typographical errors. By amendment herein, these errors have been corrected, thereby obviating the objections.

35 U.S.C. 112, First Paragraph, Enablement

Claims 1-40 and 42-47 remain rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification as filed. In particular, it is alleged that while the specification is enabling for (1) an expression cassette comprising a polynucleotide sequence encoding a Pol polypeptide as set forth in SEQ ID NO:30, 31 or 32; (2) the expression cassette of (1) further comprising a sequence encoding a viral polypeptide selected from Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof; (3) a method for generating an immune response in a

mammal comprising intramuscularly administering the expression cassette of (1) to the mammal; (4) the expression cassette of (1) further comprising one or more nucleic acids encoding one or more viral polypeptides or antigen, but that it does not reasonably provide enablement for the rest of disclosure. (Office Action, page 3). It is alleged that it would require undue experimentation to make and/or use sequences having at least 90% identity to those presented as SEQ ID NOs:30-32. (Office Action, page 10). In addition, the Examiner again cites various references in support of the enablement rejection, alleging that the state of the art in vaccines is unpredictable. (Office Action, pages 3-18).

Applicants traverse the rejections and supporting remarks.

Before addressing each issue raised by the Office, Applicants note the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Whenever the PTO makes a rejection for failure to teach how to make and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts Applicants' claim:

> the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

For the reasons detailed in the Response filed October 18, 2002, Applicants traverse the rejection. Furthermore, Applicants direct the Examiner's attention to the attached Rule 132 Declaration, filed in the parent application USSN 09/475,704, in which Dr. John Donnelly notes that it would have been routine to determine sequences having at least 90% identity to other sequences, given the disclosure of the specification:

> 7. In December 1999, the quantity of experimentation required to identify sequences exhibiting 90% identity to SEQ ID NOs:1-4 was quite low. For example, BLAST software programs were commonly known and readily available on the Internet at this time. This set of programs allows for an easy alignment and determination of percent identity as between any sequences. The skilled worker could have easily used the BLAST or any number of other similar programs to determine the percent identity between sequences (in this case between any given sequence and those presented SEQ ID NOs:1-4). The specification also provides

extensive guidance in this regard, for example, on page 17, line 3 through page 19. Working examples are also provided, for example comparisons of the claimed sequences to wild-type HIV sequences. (See, Figure 5). Furthermore, the skilled worker could have readily generated any sequence falling within the scope of the claims using routine methods, for example by utilizing PCR to generate sequences, by introducing point mutations and the like. Thus, it is my opinion that it would have required only routine experimentation to determine sequences falling within the 90% identity, as claimed.

In addition, with regard to methods of generating an immune response, Dr. Donnelly n notes:

11. Similarly, the specification as filed clearly provides ample guidance on how to generate an immune response (humoral and/or cellular) in a subject by administering the claimed sequences. (See, page 7, lines 9 to 20; page 12, line 28 to page 13, line 15; and Examples 4 and 7). Indeed, in December 1999, it was predictable and routine to evaluate whether an immune response was generated against a polypeptide antigen encoded by an administered polynucleotide, for example using the techniques and tools described above in paragraph 8. Furthermore, the skilled worker would know that generating an immune response does not necessarily mean that the subject will be vaccinated – *i.e.*, protected against HIV infection or derive some therapeutic benefit. The skilled worker would also have known that immune responses are useful for numerous scientific purposes, such as laboratory assays, preparing reagents for virologic and immunologic studies, analyzing immune responses, and preparation of diagnostic kits. Therefore, a skilled worker would have known that the claimed sequences could be used for additional scientific purposes other than seeking protective immunity or a therapeutic benefit. In view of the guidance in the specification, the predictability and state of the art, and high level of the skilled worker, it is plain that it would have been routine to administer a polynucleotide and evaluate whether or not an immune response to the encoded polypeptide was generated in the subject.

12. Moreover, in the course of further work on HIV, the inventors have evaluated the immune responses generated upon administration of the claimed Gag-encoding polynucleotide constructs to subjects. The manuscript attached hereto (Exhibit B) shows that the claimed expression cassettes generate both humoral and cellular responses when made and administered to animal subjects as described in the specification. (See, for example, Figures of Exhibit B and text describing these Figures). Specifically, this manuscript demonstrates that neutralizing

antibodies develop more rapidly in animals vaccinated with the claimed constructs; that these neutralizing antibodies correlated with lower peak viremia after pathogenic virus challenge; and that the claimed Gag-encoding constructs generate cellular immune responses. Thus, although not required by the claims, the claimed constructs are, in fact, able to generate potentially "protective" immune responses. Accordingly, a skilled worker could readily practice the claimed methods of generating an immune response in view of the teachings of the specification and state of the art as filed.

Further, concerning cell types, Dr. Donnelly states:

13. It would have also been routine to express the claimed Gag-encoding polynucleotides in stem cells or lymphoid progenitor cells. The guidance in the specification in this regard is extensive. (See, Section 2.3.2 starting on page 61 of the specification). In addition, the level of skill in this field was very high at the time of filing, the state of the art sophisticated and the experimentation needed to get expression in lymphokine cells (such as stem cells and lymphoid progenitor cells) was routine using standard vectors (*e.g.,* plasmids such pBR322 and pBLUESCRIPT that include promoters and other control elements). Even a reference cited in the Office Action makes it clear that heterologous HIV polypeptide-encoding sequences can readily be introduced into and expressed in stem cells:

Other areas where gene transfer into hematopoietic cells is being investigated include human immunodeficiency virus (HIV) infection ... the importance of these studies cannot be over emphasized as they provide 'proof-in-principle' that gene-marked cells can survive and be expressed for extended periods of time once re-introduced into the host. (Prince, *Pathology* 30:335-347 at page 340, left column, emphasis added).

Therefore, the specification teaches a skilled worker how to express the claimed Gag-encoding sequences in stem cells or progenitors of lymphoid cells.

Finally, with regard to delivery, Dr. Donnelly notes:

14. Finally, I believe that, following the teachings of the specification and guidance of the art, a skilled worker could have readily administered the claimed nucleic acids specification by a variety of modes including intramuscular, intradermal, mucosal and the like. The quantity of experimentation required to use alternatives to intramuscular delivery routes was quite low in December 1999. A skilled worker could have easily administered polynucleotides by a variety of routine methods known at the time of filing. For example, administration of polynucleotides encoding

> HIV antigens via intradermal and mucosal modes is described in Shiver et al. 1997 *Vaccine* 15:884-887 (Exhibit C) and Durrani et al. 1998 *J. Immunol. Methods* 220:93-103 (Exhibit D). These references are clearly representative of the high level of skill in the art and the fact that non-intramuscular modes of administration were considered predictable in December 1999 -- many of the examples gene delivery modes were also known. Furthermore, at the time of filing, it was known in the art that administration of polynucleotide vaccines by diverse routes such as intradermal, transdermal, intranasal, oral and the like did not require special modifications to the coding sequence of the polynucleotide plasmid construct itself. The specification provides significant direction in these regards as well, for example on page 61 of the specification. Therefore, a skilled worker would have found the claimed expression cassette and sequences at least 90% identical to it to be useful for generating an immune response using diverse routes and methods. Thus, to the skilled worker, administering the claimed polynucleotides by any number of delivery routes would have been routine and required only minor experimentation.

In sum, although Dr. Donnelly's statements focus on Gag-encoding sequences of the parent application, his conclusions are <u>all</u> equally applicable to the claimed Pol-encoded sequences.

<u>Information Disclosure Statement</u>

Applicants wish to bring to the attention of the Patent Office the references listed on the attached PTO-1449 form and request that they be considered by the Examiner. Each of the references cited on the attached was previously cited by or submitted to the PTO in prior application Serial No. 09/475,704, filed December 30, 1999, therefore no copies are enclosed. The information listed on the attached PTO-1449 forms may be material to the examination of the above-identified application. The Examiner is respectfully requested to make this information of official record in the application.

This Information Disclosure Statement under 37 CFR §1.97 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) An expression cassette, comprising

a polynucleotide sequence encoding a polypeptide including an [antigenic] immunogenic HIV *Pol* polypeptide, wherein the polynucleotide sequence encoding said *Pol* polypeptide comprises a sequence having at least 90% sequence identity to the sequence presented of Figure 8 (SEQ ID NO:30); Figure 9 (SEQ ID NO:31); or Figure 10 (SEQ ID NO:32).